

Remarks

The February 10, 2004 Official Action has been carefully reviewed. In view of the amendments submitted herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset it is noted that a shortened statutory response period of three (3) months was set in the February 10, 2004 Official Action. Therefore, the initial due date for response was May 10, 2004. A petition for a 2 month extension of the response period is presented with this response, which is being filed within the two month extension period.

At page 3 of the Official Action, the Examiner has maintained the objection to the specification for allegedly missing a structure at page 94. Applicants have amended the specification to reference Formula II. Support for this amendment can be found throughout the specification including at page 12, line 14 through page 13, line 7, where TKL analogues are described, and at page 96, line 7 through page 97, line 17, where a PKS gene is described which is similar to the one producing the compounds described at page 94, lines 5-26 (Example 48). Indeed, the chemical structures on page 97 are described as (Ac)4-nor-TKL and 4-nor-TKL, which are the compounds generated in Example 48. However, the description of (Ac)4-nor-TKL and 4-nor-TKL at page 94, lines 5-10 references R₁, R₂, and R₃ substituents. Notably, Formula II is a chemical structure of a TKL analog comprising R₁, R₂, and R₃ substituents which, upon inserting the substituents provided at page 94, lines 7-10 into the formula, yields the chemical structures of (Ac)4-nor-TKL and 4-nor-TKL at page 97. Accordingly, Applicants submit that the amendment to the specification does not introduce new matter and clarifies the gap originally present at page 94 of the specification.

The Examiner has maintained the rejection of claims 54 and 61 and newly rejected claims 25, 27, 31-37, 39, 44, 47-

58, and 60-70 under 35 U.S.C. §112, second paragraph for alleged indefiniteness on various grounds.

At pages 7, 12, and 13 of the Official Action, the Examiner has maintained the rejection of claims 62 and 63 and newly rejected claims 69 and 70 under 35 U.S.C. §112, first paragraph for allegedly containing new matter.

The rejection of claim 1 under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,962,290, has been maintained. The Examiner has also newly rejected claims 31-37, 39, 47-49, 55-58, 60, 61, and 64-67 under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,962,290.

Claims 2, 25, 44, and 68 also remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 5,962,290 in view of MacNeil et al. (Ann. NY Acad. Sci (1994) 721:123-132). Claim 27 also stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 5,962,290 in view of MacNeil et al. and further in view of Kao et al. (Science (1994) 265:509-512). The Examiner has also maintained the rejection of claims 51 and 52 under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 5,962,290 in view of MacNeil et al. and in view of U.S. Patent 5,190,871.

The foregoing objections and rejections constitute all of the grounds set forth in the February 10, 2004 Official Action for refusing the present application.

In accordance with this amendment, claims 1, 2, 52-55, 60, and 67-69 have been cancelled. All of the rejections outstanding with respect to these claims are, therefore, rendered moot. The cancellation of claims 1, 2, 52-55, 60, and 67-69 should not be construed as indicative of Applicants' concurrence or acquiescence in the various rejections of claims 1, 2, 52-55, 60, and 67-69 as set forth in the February 10, 2004 Official Action, or otherwise as an abandonment of Applicants' efforts to secure patent protection on the subject

matter of claims 1, 2, 52-55, 60, and 67-69. To the contrary, Applicants vigorously dispute those grounds of rejection. Such arguments as Applicants have to advance in rebuttal, however, are being reserved for a continuing application, which is expected to be filed and include claims directed to the subject matter of cancelled claims 1, 2, 52-55, 60, and 67-69.

Claims 25, 27, 31, 32, 35-37, 44, 47, 50, 51, 56, 61-64, and 70 are currently amended. The amendments to claim 25, 27, 31, 35-37, 44, 47, 50, 51, 56, 64, and 70 are intended to 1) change the claim dependency from cancelled claims 67 or 69 to claim 63 and 2) reword the claims to provide appropriate antecedent basis for the claimed gene assembly of claim 63. In the interest of clarity, claim 31 has been additionally amended to recite "a nucleic acid comprising" instead of "nucleic sequence encoding" because nucleic sequences do not "encode" a gene as originally written. Accordingly, claim 32 has also been amended to refer to the "nucleic acid" of claim 31, for consistency of claim terminology. Claims 61-63 have been amended to recite a "gene assembly" instead of a "gene," support for which can be found, for example, at page 6, lines 28-35; page 7, lines 14-17; page 9, lines 30-32; and page 10, lines 12-16. Claim 61 has been additionally amended to more closely reflect the definition of combinatorial module provided at page 2, lines 9-13. Claim 62 has been additionally amended to delete the "ketide type" language from the claim. Support for this amendment can be found, for example, at page 11, lines 29-35. Lastly, claim 64 has been additionally amended to remove reference to *S. coelicolor*. Support for this amendment can be found at, for example, page 10, lines 17-21.

No new matter has been introduced into this application by reason of any of the amendments presented herewith.

**CLAIMS 25, 27, 31-37, 39, 44, 47-58, AND 60-70, AS AMENDED,
MEET THE REQUIREMENTS UNDER 35 U.S.C. §112, SECOND PARAGRAPH**

The Examiner has maintained the rejection of claims 54 and 61 and newly rejected claims 25, 27, 31-37, 39, 44, 47-58, and 60-70 under 35 U.S.C. §112, second paragraph for alleged indefiniteness on the following grounds.

First, the Examiner has maintained the position that claim 54 is indefinite for recitation of the phrase "enzyme from the rapamycin system which, in said system, effects connection of the polyketide chain to an amino acid chain in place of said thioesterase." Applicants continue to disagree with the Examiner for the reasons presented in the Official Action response submitted December 22, 2003. However, in the interest of expediting prosecution of the instant application, Applicants have cancelled claim 54, thereby obviating the instant rejection.

Second, the Examiner maintains that claim 61 is indefinite for recitation of the term "combinatorial module." Specifically, the Examiner contends that, according to the definition in claim 61, a combinatorial module can be a module that is repugnant to the art accepted definition of "module," i.e., minimally a ketosynthase (KS) domain followed by an acyl transferase (AT) domain followed by an acyl carrier protein (ACP) domain. The Examiner also asserts that the claim is "beyond understanding of one of ordinary skill in the art." Applicants respectfully disagree.

At the outset, Applicants submit that it is a well-established principle in patent law that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). An applicant may also be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage. In re Hill, 161 F.2d 367, 73 USPQ 482

(CCPA 1947). However, it is also well-established that a patentee may use terms in a manner contrary to or inconsistent with one or more of their ordinary meanings. Hormone Research Foundation Inc. v. Genentech Inc., 904 F.2d 1558, 15 USPQ2d 1039 (Fed. Cir. 1990).

Applicants submit that the term "module" or "natural module," as used in the instant application at page 2, lines 5-9, can be used to refer to a set of contiguous domains minimally comprising the domains KS-AT-ACP, in order, which are capable of accomplishing one cycle of polyketide chain extension. However, Applicants draw the Examiner's attention to the fact that "natural modules" may also contain other domains, such as a dehydratase (DH) domain, that interrupt the KS-AT-ACP series of domains. Thus, a "module" or "natural module" is flexible in terms of its contents.

Additionally, Applicants also respectfully point out that the term "module" has a much more general definition. Indeed, a common definition for the term "module" is "a unit[, in a protein or nucleic acid,] of structure or function that is used in a variety of different contexts" (Alberts et al. Molecular Biology of the Cell, 3rd Ed., Garland Publishing Inc., New York, 1994, p.G-15). Applicants respectfully submit that the term "combinatorial module" is not repugnant to either of the two above-cited definitions, for the reasons discussed below.

The concept of a "combinatorial module" was not previously defined in the art. According to the MPEP at §2173.05(a):

Courts have recognized that it is not only permissible, but often desirable, to use new terms that are frequently more precise in describing and defining the new invention. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Although it is difficult to compare the claimed invention with the prior art when new terms are used that do not appear in the prior art, this does not make the new terms indefinite.

New terms are often used when a new technology is in

its infancy or is rapidly evolving. The requirements for clarity and precision must be balanced with the limitations of the language and the science. If the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the statute (35 U.S.C. 112, second paragraph) demands no more.

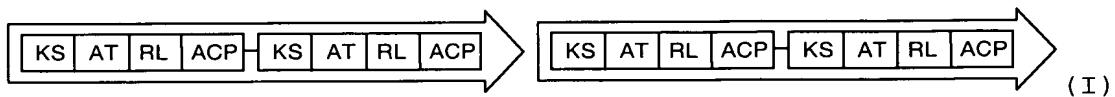
Shatterproof Glass Corp. v. Libbey Owens Ford Co., 758 F.2d 613, 225 USPQ 634 (Fed. Cir. 1985) [and] Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986).

Applicants have defined "combinatorial module" in the specification at, for example, page 2, lines 9-13. Specifically, a combinatorial module is "any group of contiguous domains (and domain parts), extending from a first point in a first natural module, to a second equivalent point in a second natural module." Thus, while a "combinatorial module" does not necessarily contain the KS-AT-ACP order of domains as in a "natural module," Applicants submit that the term "combinatorial module" is not repugnant to the term "module" because a "combinatorial module" still consists of the KS, AT, and ACP domains and an artisan of ordinary skill would recognize that the term "**combinatorial** module" must differ from a "natural module." Furthermore, Applicants submit that the term "combinatorial module" is also clearly consistent with the broader definition of "module," as the above definition of "combinatorial module" encompasses a unit of protein with a structure which can be used in a variety of contexts.

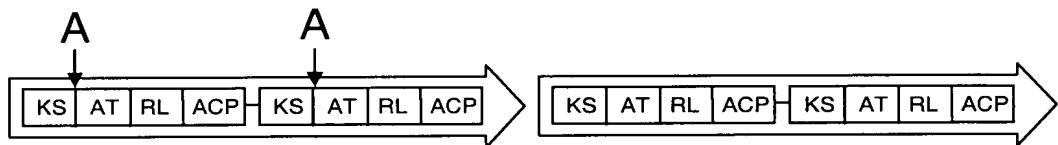
It is also the Examiner's position that claim 61 is "beyond understanding of one of ordinary skill in the art." Applicants respectfully disagree and offer the following explanation of the meaning of "combinatorial module," with reference to the diagrams shown below.

Formula I below is a hypothetical type I PKS where KS = ketosynthase, AT = acyltransferase, RL = reductive loop

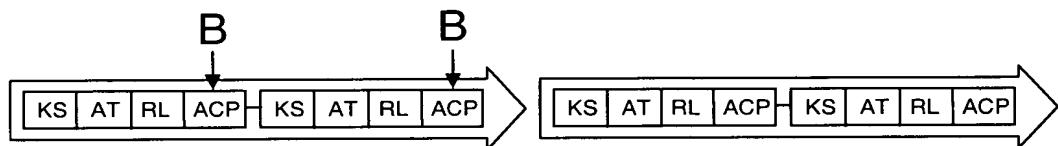
(optionally comprising hetoreductase (KR), dehydratase (DH) and enoylreductase (ER) domains), and ACP = acyl carrier protein. Each KS...ACP group of domains represents one natural module and each arrow represents one open reading frame.



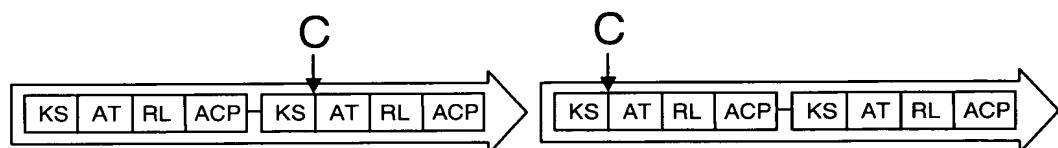
"Combinatorial modules," as defined by Applicants in the instant application, include groups of domains as shown below in Schemes A to D:



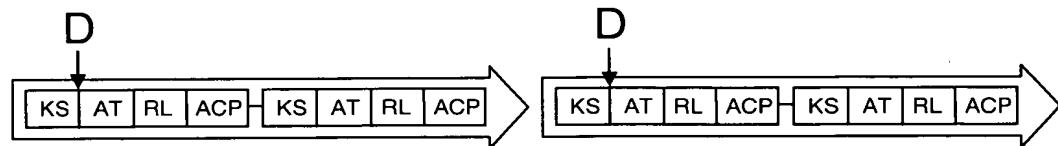
Scheme A: The combinatorial module is from the start of one domain (e.g. AT) to the start of the corresponding domain in the next module.



Scheme B: The combinatorial module is from a point within a domain (e.g. within an ACP domain) to the corresponding point within the same domain of the next module.



Scheme C: The combinatorial module is from a corresponding point in one module to the corresponding point in the next module in the next ORF. As with Schemes A and B, the replacement combinatorial module is one section of continuous DNA and includes the non-coding region between the ORFs.



Scheme D: The combinatorial module comprises more than one set of domains. Specifically, the combinatorial module is from the start of one domain (e.g. AT) to the start of the corresponding domain in a more distant module. It is noteworthy that the open-reading frames of PKS gene clusters are adjacent and therefore it is possible to construct these "combinatorial modules" by cutting at the two corresponding points and splicing in this section of DNA, as indicated by Scheme D.

Applicants submit that the four schemes illustrated above are clearly within the definition provided at page 2, lines 9-13 as being "any group of contiguous domains (and domain parts), extending from a first point in a first natural module, to a second equivalent point in a second natural module."

In light of the foregoing, Applicants submit that the claim 61 is clear as written. However, Applicants have amended the claim to more closely conform to the definition provided at page 2, lines 9-13 for clarity purposes. Thus, Applicants respectfully request that the rejection of claim 61 for alleged indefiniteness be withdrawn.

Third, the Examiner contends that claim 25 is indefinite because the term "said loading module" allegedly lacks antecedent basis. Applicants have amended claim 25 to depend from claim 63 which clearly recites a "loading module." Accordingly, Applicants respectfully request that the rejection of claim 25 for alleged indefiniteness be withdrawn.

Fourth, the Examiner asserts that claims 25, 27, 31-37, 39, 44, 47-58, and 60-70 are indefinite for recitation of the term "functional polyketide synthase." Specifically, the Examiner contends that "none of the instant claims require a "complete" PKS whose function would be to produce a polyketide." Applicants strenuously dispute the Examiner's position on the point. The Examiner's attention is respectfully directed to claim 35, for example, which is drawn to the hybrid polyketide synthase encoded for in claim 63 and claims 39 and 64 which are drawn to making polyketides from

the polyketide synthases encoded for in claim 63. Furthermore, the abstract of the instant application, as originally filed, recites that "a hybrid type I polyketide synthase gene typically containing a starter module and a plurality of heterologous extender modules is used to synthesize novel polyketides." Thus, Applicants submit that it is clear from the present specification that the term "hybrid polyketide synthase (PKS) gene," as recited in claims 61-63, refers to the entire PKS gene assembly/cluster. However, in the interest of clarity, Applicants have amended claims 61-63, from which the other pending claims ultimately depend, to recite a PKS gene **assembly**. Support for this amendment can be found throughout the application including, for example, at page 6, lines 28-35; page 7, lines 14-17; page 9, lines 30-32; and page 10, lines 12-16. Inasmuch as it is self-evident that the function of a polyketide synthase encoded by a polyketide synthase gene assembly is to produce a polyketide, Applicants submit that the term "functional polyketide synthase" cannot reasonably be held to be indefinite.

Fifth, it is the Examiner's position that claim 63 is indefinite for allegedly being drawn to a protein comprising parts a) and b) which are nucleic acids. Claim 63, as amended, is clearly drawn to a PKS **gene** assembly which is a nucleic acid and items (a) and (b) refer to nucleic acids which encode for certain portions of the PKS protein. Inasmuch as items (a) and (b) are nucleic acids and the claim is drawn to a nucleic acid, Applicants submit the instant rejection is untenable and respectfully request its withdrawal.

Sixth, the Examiner has rejected claims 64 and 65 for both including and excluding *S. coelicolor* in the group of host microorganisms. Accordingly, Applicants have amended claim 64, upon which claim 65 depends, to delete *S. coelicolor*

from the group of host microorganisms, thereby obviating the Examiner's rejection. Support for this amendment can be found at page 10, lines 17-21.

Lastly, the Examiner has rejected claim 70 for allegedly lacking antecedent basis for the PKS in the preamble of the claim. Applicants have amended the claim to refer to the gene assembly encoding the synthase. Additionally, the claim has been amended to depend from claim 63, thereby providing antecedent basis for the term "hybrid polyketide synthase gene assembly."

In light of all of the foregoing, Applicants submit that the rejection of claims 25, 27, 31-37, 39, 44, 47-58, and 60-70 under 35 U.S.C. §112, second paragraph for alleged indefiniteness is untenable and request its withdrawal.

CLAIMS 62, 63, 69, AND 70, AS AMENDED, SATISFY THE WRITTEN DESCRIPTION REQUIREMENT OF 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has maintained the rejection of claims 62 and 63 and newly rejected claims 69 and 70 under 35 U.S.C. §112, first paragraph for allegedly containing new matter in the sense that the subject matter of the rejected claims lacks a written description in the application as originally filed.

Specifically, the Examiner contends the specification fails to describe the production of specific ketide types, as allegedly required by claims 62 and 63. Applicants respectfully disagree. Claim 62 calls for a first nucleic acid portion encoding a plurality of modules including a first extension module which "produces a ketide unit of a first type." Claim 62 further recites replacing the first extension module with a second extension module which produces a "ketide unit of a second type," wherein the ketides differ in either oxidation state, stereochemistry, and substitution pattern. Applicants respectfully submit that at page 8, lines 1-4, the instant specification plainly teaches that extension

modules may be replaced by "one that gives a ketide unit at a different oxidation state and/or with a different stereochemistry" (see also page 11, lines 29-35). Additionally, original claim 10 is drawn to replacing extension modules leading to a ketide unit with a different extension module leading to a ketide unit which differs in "oxidation state and /or stereochemistry and/or substitution pattern." However, for clarity purposes, Applicants have amended claim 62 to recite a "first ketide unit" and a "second ketide unit" and eliminated the "ketide type" language from the claim.

Additionally, it should be noted that claim 63 does not recite the ketide type limitations present in claim 62. Indeed, claim 63 does not even recite the word ketide. Therefore, Applicants submit that "producing specific ketide types" is **not** a "clear limitation" in claim 63 as asserted by the Examiner. For completeness, Applicants reiterate that support for claim 63 can be found throughout the specification at, for example, page 9, lines 5-19 and Example 32. Accordingly, Applicants respectfully request the withdrawal of the rejection of claim 63 under 35 U.S.C. §112, first paragraph.

The Examiner also asserts that claims 69 and 70 contain new matter. Specifically, it is the Examiner's position that the specification fails to provide adequate support for the phrase "loading module lacking a ketosynthase (KS) domain." Applicants continue to take issue with the Examiner's position for the reasons presented in the Official Action response submitted December 22, 2003. However, in an effort to expedite prosecution of the instant application, Applicants have cancelled claim 69 and amended claim 70 to depend from claim 63, neither of which contains the above-mentioned phrase.

For all of the foregoing reasons, Applicants

respectfully submit that the rejection of claims 62, 63, and 70 under 35 U.S.C. §112, first paragraph for allegedly containing new matter is untenable and request its withdrawal.

**CLAIMS 1, 31-37, 39, 47-49, 55-58, 60, 61, AND 64-67 ARE NOT
ANTICIPATED BY U.S. PATENT 5,962,290**

The Examiner has maintained the rejection of claim 1 under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,962,290. The Examiner has also newly rejected claims 31-37, 39, 47-49, 55-58, 60, 61, and 64-67 under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,962,290.

Applicants continue to disagree with the Examiner's expansive interpretation of U.S. Patent 5,962,290 for the reasons set forth in the Official Action response filed December 22, 2003 and in previous Official Action responses. However, Applicants have cancelled claims 1, 55, 57, 60 and 67 and amended dependent claims 31-37, 39, 47-49, 56, 58, and 64-66 to depend from claim 63 instead of cancelled claim 67. Notably, claim 63 is not deemed by the Examiner to be anticipated by U.S. Patent 5,962,290. Accordingly, Applicants submit that the rejection of claims 1, 31-37, 39, 47-49, 55-58, 60, and 64-67 under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,962,290 has been overcome.

With regard to claim 61, Applicants submit that U.S. Patent 5,962,290 fails to teach a combinatorial module as recited by claim 61. Specifically, claim 61, as amended, is drawn to a hybrid PKS comprising a **combinatorial** module, wherein the combinatorial module is a "sequence extending from a **first point** in a first natural module to a **second point** at the **corresponding position** in a second natural module." The Examiner relies on claim 10 of U.S. Patent 5,962,290 in support of the argument that the '290 patent teaches recombinant Type I PKS wherein the activities (e.g., ketosynthase activity, acyl carrier protein activity, acyl

transferase activity, and others) of the PKS are derived from at least two different PKSs. Claim 10 and the specification of U.S. Patent 5,962,290, however, are silent with regard to a module extending from a first point in one module to a second point at the corresponding position in another module, as required by claim 61 of the instant application. Inasmuch as U.S. Patent 5,962,290 fails to teach each and every aspect of the instantly claimed invention, Applicants submit that the rejection of claim 61 under 35 U.S.C. §102(e) as anticipated by U.S. Patent 5,962,290 is untenable.

In light of the foregoing, Applicants respectfully request that the rejection of claims 31-37, 39, 47-49, 56, 58, 61, and 64-66 under 35 U.S.C. §102(e) be withdrawal.

**CLAIMS 2, 25, 27, 44, 51, 52, AND 68 ARE NOT RENDERED OBVIOUS
BY U.S. PATENT 5,962,290 IN VIEW OF MACNEIL ET. AL., KAO ET
AL., AND/OR U.S. PATENT 5,190,871**

The Examiner has maintained the rejection of claims 2, 25, 44, and 68 under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 5,962,290 in view of MacNeil et al. (Ann. NY Acad. Sci (1994) 721:123-132). Claim 27 also stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 5,962,290 in view of MacNeil et al. and further in view of Kao et al. (Science (1994) 265:509-512). The Examiner has also maintained the rejection of claims 51 and 52 under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 5,962,290 in view of MacNeil et al. and in view of U.S. Patent 5,190,871.

Applicants continue to disagree with the Examiner's position for the reasons set forth in the Official Action response filed December 22, 2003. However, Applicants have deleted claims 2, 52, and 68 and amended claims 25, 27, 44, and 51 to ultimately depend from claim 63. Notably, claim 63 is presumptively free of the prior art cited by the Examiner.

Accordingly, Applicants submit that the rejections of claims 25, 27, 44, and 51 under 35 U.S.C. §103(a) are obviated and Applicants respectfully request their withdrawal.

CONCLUSION

It is respectfully requested that the foregoing remarks and amendments presented herewith be entered in this application, since it is believed they clearly place the pending claims in condition for allowance. In any event, the claims as presently amended are believed to eliminate certain issues and better define other issues which would be raised on appeal, should an appeal be necessary in this case. These amendments were not presented earlier, because the arguments to which they respond, for the most part, were advanced for the first time in the February 10, 2004 Official Action.

In view of the amendments presented herewith, and the foregoing remarks, it is respectfully urged that the objections and rejections set forth in the February 10, 2004 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number give below.

Respectfully submitted,
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